

Rebuttal
Trends in Therapy**Drug Spotlight****BEST AVAILABLE COPY**

Corticosteroid Therapy

I. Pharmacological Properties and Principles of Corticosteroid Use

David H. P. Streeten, MB, D Phil, MRCP

SINCE cortisone and corticotropin first became available more than 25 years ago, these agents, and particularly the newer synthetic corticosteroids, have established an important place for themselves in the therapy of a wide variety of disorders falling within the purview of virtually every branch of medical practice. Surprisingly, however, there is still uncertainty about the role of steroid therapy in several specific disease states. There are also some important recent advances of a practical nature that make it worthwhile to review the modern use of steroid therapy in clinical practice.

PHARMACOLOGICAL PROPERTIES

Corticosteroids have widely differing actions on the tissues and fluids of the body, and many of their effects may be considered therapeutically valuable in one patient and unwarranted side effects in another. Thus, the effect of raising blood glucose levels may be an important reason for using a glucocorticoid in a patient with adrenal insufficiency or, temporarily, in an individual with an islet cell adenoma of the pancreas, yet may be disadvantageous in aggravating

latent diabetes mellitus in other patients.

General Actions of Corticosteroids

Anti-inflammatory and Antiallergic Actions.—Steroids nonspecifically inhibit the inflammatory effects of many noxious agents, including microorganisms, chemical or thermal irritants, trauma, and allergens. The anti-inflammatory actions of corticosteroids comprise (1) reduction of the exudation of leukocytes and plasma constituents, thereby lessening edema; (2) maintenance of cellular membrane integrity with consequent prevention of excessive swelling of the cells; (3) inhibition of lysozyme release from granulocytes and inhibition of phagocytosis in other ways; and (4) stabilization of the membranes of the intracellular lysosomes, which contain hydrolytic enzymes capable of cell digestion and extension of inflammatory tissue damage. The fibroblastic proliferation, which follows inflammation as part of the reparative process and tends to localize infection, is greatly reduced by corticosteroids that may thus potentiate the spread of an infection, or may be beneficial in preventing the adverse consequences of excessive fibrosis. Corticosteroids in usual clinical doses also impair cellular immune responses, such as the delayed-type skin reactions to tuberculin and histoplasmin, and in massive doses they may

have some effect on antibody formation, though this has not yet been clearly demonstrated in man. These actions may predispose individuals treated with large doses of corticosteroids to repeated infections, but may also be the basis of the therapeutic efficacy of steroids in autoimmune disorders and in suppressing the inflammatory response of the recipient to organ transplants.

Effects on Protein and Carbohydrate Metabolism.—The glucocorticoids inhibit the transport of amino acids into muscle and reduce new protein synthesis (antianabolic effect). The utilization of amino acids by the liver for gluconeogenesis requires the presence of cortisol, and this effect of glucocorticoids is an important component of the physiological adjustments that maintain the level of blood glucose during starvation. Enhancement of gluconeogenesis probably also contributes to the diabetogenic side effects of steroid therapy.

Steroid Actions on Water and Electrolytes.—All of the corticosteroids tend to cause hypokalemia by increasing urinary losses of potassium. Sodium retention is potentiated very strikingly by the mineralocorticoids (aldosterone, fludrocortisone, deoxycorticosterone), slightly or moderately by the natural glucocorticoids (hydrocortisone, corticosterone), and negligibly by most of the synthetic glucocorticoids (prednisone, prednisolone).

From the Section of Endocrinology, Department of Medicine, State University of New York Upstate Medical Center, Syracuse, NY.

Reprint requests to Department of Medicine, Upstate Medical Center, 750 E Adams St, Syracuse, NY 13210 (Dr. Streeten).

lone, dexamethasone), while a few steroids actually enhance sodium excretion (triamcinolone, betamethasone, methylprednisolone). The mineralocorticoids tend to enhance retention of water together with sodium, but the glucocorticoids (except corticosterone) increase free-water clearance and promote water excretion in man, partly by inhibiting the release of antidiuretic hormone and partly perhaps by a direct action on the renal tubule. These actions and reduction of the cellular water content contribute to the mechanisms whereby steroid therapy restores the serum sodium concentration to normal when administered to patients with adrenal insufficiency. Edema, a relatively frequent side effect of treatment with cortisone, is seldom seen when the synthetic steroids are used.

Actions on the Central Nervous System.—Glucocorticoids increase the excitability of the brain cortex, perhaps by increasing the sodium content of the glial cells. Electroencephalographic slowing seen in adrenal insufficiency is corrected by hydrocortisone. Excessive doses of glucocorticoids lower the threshold to electric shock in animals and may increase the frequency of convulsive seizures in human patients who have epilepsy. Most of the glucocorticoids (except triamcinolone) tend to increase appetite and this effect may be considered beneficial or deleterious depending on whether the patient is anorexic or has a tendency to obesity.

Effects on the Blood Cells.—Glucocorticoids have important effects on the lymphocytic, granulocytic, erythrocytic, and thrombocytic systems: lymphocytic tissues are suppressed, and the numbers of circulating lymphocytes are diminished. These actions form the basis of the clinical use of steroid therapy in lymphocytic leukemias and lymphosarcoma. Hydrocortisone and its analogues also suppress the phagocytic activity of the reticuloendothelial system.

All these actions constitute the rationale for the use of corticosteroid therapy in prolonging the life-span of platelets in thrombocytopenia, of granulocytes in some granulocytopenias, and of erythrocytes in

patients with autoimmune hemolytic anemia.

DIFFERENCES

The anti-inflammatory potencies of the glucocorticoids are approximately equal when these agents are used in the same multiples of the doses contained within the commonly dispensed tablets. Thus, 25 mg of cortisone is roughly equivalent in glucocorticoid effect to 20 mg of hydrocortisone, 5 mg of prednisone or prednisolone, 4 mg of methylprednisolone or triamcinolone, 0.75 mg of dexamethasone, and 0.6 mg of betamethasone. There are differences in the duration of action of the corticosteroids that are of therapeutic importance, particularly when alternate-day therapy is used.

Parenteral Therapy

When steroids are administered intramuscularly, the rapidity of onset of therapeutic effects is directly related to the solubility of the compounds used. The highly water-soluble esters (hydrocortisone sodium succinate, hydrocortisone sodium phosphate, methylprednisolone sodium succinate, dexamethasone sodium phosphate) are rapidly absorbed, producing high blood levels within 15 to 30 minutes. The water-soluble hydrocortisone esters are rapidly metabolized, so that therapeutically effective blood levels cannot be maintained unless these compounds are given approximately every two hours intramuscularly or, preferably, by continuous intravenous infusion. When the most intense anti-inflammatory effect is desired, it is best to give one of the water-soluble corticoids by intravenous injection (eg, 100 mg of hydrocortisone), followed by a constant intravenous infusion, usually in doses equivalent to 10 to 15 mg of hydrocortisone per hour, in 5% dextrose or 0.9% saline solution.

Unesterified hydrocortisone (or hydrocortisone with free alcohol) when administered intramuscularly as an aqueous suspension (eg, Cortef) establishes therapeutically useful blood levels within three to four hours that can conveniently be maintained by six-hourly injections. Cortisone ac-

tate is less water soluble and at present has little to commend its parenteral use. The acetates of hydrocortisone, prednisolone, methylprednisolone, and triamcinolone have such low aqueous solubility that they are most suitable for producing sustained local action by injection into inflamed joints, bursae, and tendon sheaths, or into keloids and other local inflammatory and fibrotic lesions. Occasionally these agents are useful when relatively low steroid blood levels are adequate and when intramuscular injections at prolonged intervals are preferable to daily oral administration (eg, in unreliable patients). For topical application to the skin, lotions, creams, and ointments containing hydrocortisone, triamcinolone, or betamethasone are most frequently used. Drops of aqueous solutions of water-soluble esters of hydrocortisone, prednisolone, dexamethasone, betamethasone, and triamcinolone are commonly used in inflammatory disorders of the eyes.

The 11-hydroxyl radical is necessary for most glucocorticoid effects. Those steroids that lack this radical at the C-11 position have little or no demonstrable local therapeutic action when applied to the joints, the skin, or the eyes. Since the 11-ketone group of prednisone and cortisone is rapidly and efficiently converted to an 11-hydroxyl group, mainly in the liver, prednisone and cortisone are almost as effective as prednisolone and hydrocortisone, respectively, when used systemically, as long as this hepatic function is unimpaired in the patient.

When it is imperative that sodium retention be avoided and sodium excretion potentiated—as in patients with congestive heart failure and other conditions associated with edema—triamcinolone or betamethasone are the drugs of choice. On the other hand, these drugs should not be used in patients with sodium depletion or hyponatremia.

Patients sometimes consider that one glucocorticoid is more efficacious than another when given in seemingly equipotent doses. Thus, occasionally an asthmatic patient will claim that he experiences great symptomatic relief from triamcinolone or betamethasone and rela-

tively little help from prednisolone. The objectivity of these claims and the possible underlying mechanisms have never been established but are probably worthy of future investigation.

GENERAL PRINCIPLES OF CORTICOSTEROID THERAPY

Use corticosteroid therapy only when a diagnosis has been established and when less harmful forms of therapy have failed. In many nonspecific inflammatory disorders, the physician is frequently tempted to start corticosteroid therapy before a specific diagnosis has been made. In general, this should be avoided unless and until all potentially useful diagnostic procedures have been applied or unless there is evidence of rapid deterioration that becomes dangerous or life-threatening.

Use the smallest therapeutically effective dose. Corticosteroid drugs should always be administered in a dose and by a route that will provide adequate therapeutic effect with a minimum of therapeutically undesirable "side effects." Whenever pharmacological doses of corticosteroids are needed to produce therapeutic benefit, the physician should be constantly aware of the need to reduce dosage and to determine whether a smaller dose might be equally effective. Knowledge of the usual time-course of the disease that is to be treated and careful supervision of the patient are clearly essential in order to avoid initiating a flare-up of the disorder under treatment by tapering dosage too rapidly or by too large decrements. Sometimes empiricism—using the experience gained in the individual patient—is the most satisfactory guide to an optimal dosage schedule. As part of the attempt to use the smallest doses possible, the physician is well advised to apply corticosteroids locally to the affected parts (eg, skin, bursae, joints) whenever practicable.

Use a alternate-day therapy whenever possible. An important advance in corticosteroid therapy for many disorders was made when Harter and co-workers¹ showed that intermittent (ie, less frequent than once daily) administration of glucocorticoids fre-

quently has the desired therapeutic effect with diminished side effects and less pituitary-adrenal suppression. These authors have emphasized the following important points:

(i) Alternate-day therapy usually requires that the hypothalamic-pituitary-adrenal axis be functioning normally. Thus, individuals in whom this axis has been profoundly suppressed by previous long-term, daily corticosteroid therapy, will usually have to suffer considerable discomfort on the days off treatment for several months before the full advantages of the method are realized. While waiting for the pituitary-adrenal axis to recover from its previous suppression, it is usually necessary to give on alternate days two, three, or four times the previous total daily dose. During the subsequent months, this dosage can then be gradually reduced.

(ii) It is usually advisable to control the disorder under treatment with corticosteroid administered frequently or continuously each day for a few days. When the asthma, rheumatoid arthritis, lupus erythematosus or other condition has been clearly under good control for a few days, and before suppression of the pituitary-adrenal axis has passed beyond the stage of transience, alternate-day maintenance therapy should be initiated, starting with approximately twice the initial total daily dose on alternate days, and decreasing or increasing this alternate-day dosage as required by evidence of continuing control of the underlying disease.

(iii) In alternate-day therapy the corticosteroid should be given in the morning before breakfast.

(iv) Steroids of relatively short half-life must be used in order to accomplish the potential advantages of alternate-day therapy. Thus, prednisolone is very effective, but, probably because of its longer half-life, dexamethasone suppresses the pituitary-adrenal axis for too prolonged a period to allow for its beneficial use in alternate-day therapy.

Teach patients about the need for higher steroid doses during "stress." No patient should be given corticosteroid therapy for more than a few weeks without being thoroughly indoctrinated in the need to increase corticosteroid dosage during "stresses." The spouse or closest relative or friend, and the patient, should understand that increased dosage is required during "stress," whether or not the patient is well enough to appreciate the presence of the "stress" himself/herself, and that the higher

dosage might well make all the difference between a return to health and further deterioration of his condition or even death. In addition, every patient receiving long-term corticosteroid therapy should be given a card to be kept on his/her person at all times, containing the information shown in the Figure. Many lives have been unnecessarily lost because these "educational" requirements for patients being administered corticosteroid therapy were not met.

DOSAGE-REDUCTION AND CESSATION OF THERAPY

When it is deemed necessary or advisable to reduce the dosage or to stop corticosteroid therapy completely, several important points should be observed:

Dosage should be tapered, as rapidly as possible without allowing the underlying disorder to relapse. If the disease under treatment "flares up," the corticosteroid dosage should be raised at least to the level in use before the reduction that caused the relapse. In general, pharmacological doses can be reduced without considering anything other than relapse of the disorder under treatment until the maintenance dosage required for an individual under the "stress" of the particular disorder being treated has been reached. For instance, in a patient who has received 40 mg of prednisone daily for six years for rheumatoid arthritis, the dosage can usually be reduced by 5- or 10-mg decrements every two to six days, while the physician watches for an exacerbation of the arthritis, until a total daily dose of 5 to 10 mg has been reached.

Once a daily dose that is equivalent to 5 to 10 mg of prednisone has been reached, further reduction in dosage may be rapid only if the duration of corticosteroid therapy has been short (< 6 to 12 months) or the dosage small (< 10 mg of prednisone daily). In such patients, corticosteroid therapy may frequently be terminated abruptly or after tapering the dosage for a few days without adverse consequences, since the unsuppressed hypothalamic-pituitary-adrenal system will rapidly resume normal activity. However, if corticosteroid therapy has been pro-

Card for Patient on Corticosteroid Therapy

Mr.
Mrs.
Miss _____ is being treated for _____ (disorder)
with _____ (corticosteroid) in a dose of _____ (dose) _____. In the
event of "stress", the steroid dosage should be increased thus:

1. Mild "Stress" (eg, common cold, single dental extraction, mild trauma): use double doses daily.
2. Moderate "Stress" (eg, flu, surgery under local anesthesia, several dental extractions): use hydrocortisone, 100 mg, or prednisolone, 20 mg, or dexamethasone, 4 mg daily.
3. Severe "Stress" (eg, general surgery, pneumonia or other systemic infections, high fever, severe trauma): use hydrocortisone, 200 mg, or prednisolone, 40 mg, or dexamethasone 8 mg daily.

When vomiting or diarrhea precludes absorption of oral doses, give dexamethasone 1 to 4 mg intramuscularly every 6 hours.

(Signed) _____ M.D.

(Address) _____

longed or the dosage high, one should expect that the patient's hypothalamic-pituitary-adrenal system is in a state of profound suppression, probably involving morphological atrophy. In these circumstances, prolonged gradual tapering of corticosteroid dosage over many months is necessary, since full regeneration of normal function will require the passage of 9 to 12 months, at least. There are

many acceptable ways of tapering corticosteroid dosage from maintenance levels (ie, approximately 5 mg of prednisone daily) to zero. One way is to lower the dosage every one to two months by decrements of 1 mg of prednisone per day. This allows the occurrence of symptomatically mild degrees of adrenal insufficiency that stimulate gradual regeneration of hypothalamic-pituitary-adrenal func-

tion over many months. When intermittent "stresses" (infections, trauma, surgical procedures) occur, full doses (Figure) should be resumed until the "stress" has subsided and tapering of dosage resumed thereafter. The usefulness of corticotropin therapy, aimed at restoring the mass and functional capacity of the adrenals, has been widely debated and is open to considerable doubt, since the most obstinate block after prolonged corticosteroid therapy is not at the level of the adrenal responses to corticotropin but is in the ability of the hypothalamic-pituitary unit to resume release of adequate amounts of corticotropin. This block cannot be corrected, and, in fact, is probably worsened by the use of corticotropin therapy during attempts to stop long-term corticosteroid therapy.

When corticosteroid treatment has finally been stopped, it is important to appreciate that patients are susceptible for several months to pituitary-adrenal insufficiency if subjected to "stress." For at least one year after any course of corticosteroid therapy that has lasted longer than three months, it is advisable to administer appropriate doses of corticosteroids (Figure) in the presence of infections, trauma, surgical operations, or other "stresses."

This investigation was supported by a Graduate Training Grant in Endocrinology (AM 05252) from the National Institute of Arthritis, Metabolism, and Digestive Diseases, and a Clinical Research Center grant (RR 02229) from the Division of Research Facilities and Resources, Public Health Service.

References

1. Harter JG, Reilly WJ, Thorn GW: Studies on an intermittent corticosteroid dosage regimen. *N Engl J Med* 268:501, 1963.
2. Gruber AL, Ney RL, Nicholson WE, et al: Natural history of pituitary-adrenal recovery following long term suppression with corticosteroids. *J Clin Endocrinol Metab* 25:11-16, 1962.